
REMARKS

Amendments to the Specification

The paragraph on page 1 lines 22-27 is amended herein to insert the term "polyethylene glycol" in order to to spell out in full the term "PEG" at the first instance of its use in the specification, as required by the Examiner. This amendment introduces no new matter into the specification.

Status of and Amendments to the Claims

To expedite prosecution, claims 60 and 66-72 are canceled herein without prejudice to subsequent renewal or filing in one or more divisional and/or continuation application. The claim amendments and cancellations are not to be construed as abandonment of any canceled subject matter or agreement with any objection or rejection of record.

Claims 58-59 and 61-65 are pending with entry of this amendment. Claims 58, 59 and 65 are amended herein. Support for amendments to claim 58 may be found, for example, at least on page 6 lines 17-20, page 16 lines 1-5, and in canceled claim 60. Claim 59 is amended per the Examiner's request, and claim 65 is amended to clarify the claim and to correct dependency. These amendments introduce no new matter into the specification.

Information Disclosure Statement

On page 2 of the Office Action the Examiner noted "The references listed in IDS filed 9 October 2001 and IDS filed 25 June 2002 have been received and considered."

Applicants note with appreciation the Examiner's thorough consideration of the 12 references cited in the Information Disclosure Statement filed October 9, 2001, as evidenced by the photocopy of the one-page Form 1449 initialed and signed by the Examiner which was included with the current Office Action.

However, contrary to the Examiner's statement that the references listed in the IDS filed 25 June 2002 were received and considered, it appears the two-page photocopy of the Form 1449 filed 25 June 2002 included with the Office Action was signed by the Examiner on the bottom of

each page, **but each of the 10 references listed on that Form 1449 were crossed out, and none of the 10 references were initialed by the Examiner.** If the Examiner did indeed consider the references submitted 25 June 2002 (as he had noted on page 2 of the Office Action), Applicants respectfully request a corrected copy of that Form 1449 in which each reference is initialed in the column provided, such that it is clearly indicated on the record that each reference was considered. If the Examiner requires additional copies of the ten references originally provided in the IDS submitted June 25, 2002, Applicants will gladly provide them, upon request.

Objections to the Specification and Claims

(1) The specification was objected to for the following reason: "In page 19, line 17, "PEG" should be spelled out in full at the first instance of use." It is not clear from the wording of the objection whether the Examiner requires the very first occurrence of the term "PEG" in the specification to be spelled out, or if he requires specifically the term "PEG" on page 19 line 17 to be spelled out, or both. Applicants wish to point out that the first occurrence of the term "PEG" in the specification is actually on page 1, line 24. Accordingly, the specification has been amended to spell out the very first occurrence of the term "PEG" in the specification on page 1, line 24. Applicants surmise this was the Examiner's intent, and request that the objection to the specification be withdrawn.

(2) The objection to claim 59 has been overcome by deleting "c)" from the claim, as requested by the Examiner.

Rejections under 35 USC §112 second paragraph

Claims 58-72 were rejected under 35 USC §112 second paragraph. To expedite prosecution, claims 60 and 66-72 are cancelled herein, rendering the rejection of these claims moot. The various rejections as they apply to pending claims 58-59 and 61-65 and Applicants' responses thereto are provided below.

A. Claim 58 was rejected because the Examiner found the term "contributes to" unclear, in that it is "...not clear as to whether or not the peptide participates in glycosylation by posessing the glycosylation site (*cis* action) or by an indirect mechanism wherein the peptide does not posess the glycosylation site but has an ability of stimulating or inhibiting glycosylation thereof (*trans* action)." This rejection is respectfully traversed.

Page 7 lines 3- page 8 line 2 of the specification clearly defines the term "contributes to", as follows:

> The term "contributing to a glycosylation site" as used in connection with the peptide addition X is intended to cover the situation, where a glycosylation site is formed from more than one amino acid residue (as is the case with an N-glycosylation site), and where at least one such amino acid residue originates from the peptide X and at least one amino acid residue originates from the polypeptide Pp, whereby the glycosylation site can be considered to bridge X and Pp (or, where relevant, Px or Py).

Thus the term "contributes to" is intended to pertain to the situation where, for example, for an N-glycosylation site (which has the general motif N-X'-S/T/C-X''), the N residue of the N-glycosylation site is in the peptide X, and the S,T, or C residue is in the polypeptide Pp. Without the peptide addition X, the N-glycoslyation site would not be present since the N residue of the N-glycosylation motif would not be present. To expedite prosecution, claim 58 has been amended to incorporate the limitations of claim 60, such that X comprises or contributes to an *in vivo* N-glycosylation site.

Furthermore, the term "N-glycosylation site" is defined in the specification on page 6 lines 7-11 as follows:

> An "N-glycosylation site" has the sequence N-X'-S/T/C-X'', wherein X' is any amino acid residue except proline, X'' any amino acid residue that may or may not be identical to X' and preferably is different from proline, N asparagine and S/T/C either serine, threonine or cysteine, preferably serine or threonine, and most preferably threonine. The oligosaccharide moiety is attached to the N-residue of such site.

In addition, the term "*in vivo* glycosylation" is defined in the specification on page 5 lines 26-29 as follows:

> The term "*in vivo* glycosylation" is intended to mean any attachment of an oligosaccharide moiety occurring *in vivo*, i.e., during posttranslational processing in a

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> glycosylating cell used for expression of the polypeptide, e.g., by way of N-linked and O-linked glycosylation.

Thus, for example, if the peptide addition X is one amino acid in length, that one amino acid must, according to the above definition, be an N (asparagine) residue, and the first 2 amino acids of Pp must be X' followed by S/T/C (as defined above), to form the *in vivo* N-glycosylation motif N-X'-S/T/C-X'', in which X (in this example the single amino acid N) contributes to the *in vivo* N-glycosylation site. Applicants thus respectfully submit that the term "contributes to" in pending claim 58 is clear and definite, and request the rejection be withdrawn.

B. Claim 58 was rejected because Examiner found the term "X is a peptide addition 1-30 amino acids in length" unclear, "...as to whether or not 1-30 amino acids are added to said peptide". This rejection is respectfully traversed.

Page 6 lines 17-20 of the specification clearly defines the term "peptide addition", as follows:

> The term "peptide addition" is intended to indicate one or more consecutive amino acid residues that are added to the amino acid sequence of the polypeptide Pp of interest. Normally, the peptide addition is linked to the amino acid sequence of the polypeptide Pp by a peptide linkage.

Thus the term "peptide addition" is the term used to clearly indicate the one or more consecutive amino acids (that is, 1-30 consecutive amino acids as specified by the claim), designated X, which are linked to the polypeptide Pp via a peptide linkage. However, to expedite prosecution, claim 58 has been amended to clarify that "X is a peptide addition 1-30 *consecutive* amino acids in length" and to include the phrase "wherein X and Pp are linked by a peptide linkage". Applicants respectfully submit that the term "peptide addition" in pending claim 58 is clear and definite, and request the rejection be withdrawn.

C. Claims 58, 59, 65-67 and 69-71 were rejected because the Examiner found the term "a peptide-extended polypeptide" in part a) of claim 58 unclear, allegedly because "...the specification does not define the recitations". The Examiner further queried "...does the item a)

recitation refers to a polypeptide comprising branched peptide moiety (or moieties) attached to the peptide backbone of said polypeptide through isopeptide bond formed between lysine ε-amino group and carboxyl group?" To expedite prosecution, claims 66-67 and 69-71 have been canceled, rendering rejection of these claims moot. The rejection of pending claims 58, 59 and 65 is respectfully traversed.

The term "peptide-extended polypeptide" is used in the claim to refer to the polypeptide having the structure NH_2-X-Pp-COOH, in order to distinguish that polypeptide from the polypeptide of interest Pp. The definition of the term is thus implicit in the claim itself. Furthermore, as to the Examiner's concern that the term "peptide-extended polypeptide" would encompass "a branched peptide moiety (or moieties) attached to the peptide backbone of said polypeptide through isopeptide bond formed between lysine ε-amino group and carboxyl group", it is unclear how the claim as presented, which requires expression in a glycosylating host cell of a nucleic acid comprising a nucleotide sequence encoding a peptide-extended polypeptide with the sequence NH_2-X-Pp-COOH, could possibly read on such a configuration. Nevertheless, to expedite prosecution, claim 58 has been amended as described above to recite "X is a peptide addition 1-30 *consecutive* amino acids in length" and, as noted above, the phrase "wherein X and Pp are linked by a single peptide linkage" has been added, in order to distinguish the peptide-extended polypeptide, as recited in the claim, from an arrangement involving "a branched peptide moiety (or moieties) attached to the peptide backbone of said polypeptide through isopeptide bond formed between lysine ε-amino group and carboxyl group" as asserted by the Examiner. Applicants respectfully submit that the term "a peptide-extended polypeptide" in pending claims 58, 59, and 65 is clear and definite, and request the rejection be withdrawn.

D. Pending claims 58, 59, and 65 were also rejected because Examiner found the term "a peptide-extended **glycosylated** polypeptide" in part b) of claim 58 unclear, allegedly because "...the specification does not define the recitations". The Examiner further queried "...does the item b) recitation refers to a glycosylated polypeptide comprising branched peptide moiety (or moieties) attached to the peptide backbone of said polypeptide through isopeptide bond formed between lysine ε-amino group and carboxyl group?" This rejection is respectfully traversed.

The term "peptide-extended glycosylated polypeptide" is used in the claim to refer to the polypeptide having the sequence NH_2-X-Pp-COOH which is glycosylated as a result of the nucleic acid encoding the polypeptide having the structure NH_2-X-Pp-COOH being expressed in a glycosylating host cell, as required by the claim. The definition of the term is thus implicit in the claim itself. Furthermore, as to the Examiner's concern that the term "peptide-extended glycosylated polypeptide" would encompass a "branched peptide moiety (or moieties) attached to the peptide backbone of said polypeptide through isopeptide bond formed between lysine ε-amino group and carboxyl group", it is unclear how the claim as presented, which requires expression in a glycosylating host cell of a nucleic acid comprising a nucleotide sequence encoding the sequence NH_2-X-Pp-COOH, could possibly read on such a configuration. Nevertheless, to expedite prosecution, claim 58 was amended as noted above to recite "X is a peptide addition 1-30 *consecutive* amino acids in length" and, as noted above, the phrase "wherein X and Pp are linked by a single peptide linkage" has been added, in order to distinguish the peptide-extended glycosylated polypeptide of the invention from an arrangement involving "a branched peptide moiety (or moieties) attached to the peptide backbone of said polypeptide through isopeptide bond formed between lysine ε-amino group and carboxyl group" as asserted by the Examiner. Applicants respectfully submit that the term "a peptide-extended glycosylated polypeptide" in pending claims 58, 59, and 65 is clear and definite, and request the rejection be withdrawn.

E. Claim 58 was rejected because the Examiner found the term "Pp is the polypeptide of interest" unclear. Applicants believe this rejection is overcome by the amendment to claims 58 specifying that Pp is the sequence of the mature form of the polypeptide of interest, and respectfully request the rejection be withdrawn.

F. Claim 65 was rejected because the Examiner found the term "a non-peptide moiety" unclear, allegedly because "...the specification provides insufficient definition of the non-peptide moiety". The Examiner further found the term "attachment group" unclear, asking,

"...does said (attachment) group differs form *[sic]* the glycosylation site?". Applicants respectfully traverse.

Contrary to the Examiner's assertion, the term "non-peptide moiety" is clearly described in the specification, for example, at least on page 1 lines 22-25, page 5 lines 10-19, and the table on page 7. The term "attachment group" is likewise clearly defined in the specification, for example, on page 6 lines 20-24:

> The term "attachment group" is intended to indicate a functional group of the polypeptide, in particular of an amino acid residue thereof or an oligosaccharide moiety attached to the polypeptide, capable of attaching a non-peptide moiety of interest. Useful attachment groups and their matching non-peptide moieties are apparent from the table below.

The table on on page 7 provide numerous examples of non-peptide moieties and their corresponding attachment groups.

Furthermore, claim 65 recites the following:

> The method of claim 58, further comprising:
> incubating the peptide-extended **glycosylated** polypeptide with a non-peptide moiety **which differs from an oligosaccharide moiety**, under conditions suitable to covalently attach said non-peptide moiety to an attachment group of the polypeptide.*(emphasis added)*

Claim 65 requires that the polypeptide is **already glycosylated** owing to the fact that the polypeptide was expressed in a glycosylating host cell as required in claim 58 from which claim 65 depends. Furthermore, claim 65 recites that the glycosylated polypeptide is incubated with a non-peptide moiety **which differs from an oligosaccharide moiety**. Clearly the attachment group for the "non-peptide moiety which differs from an oligosaccharide moiety" is not the glycosylation site, since the glycosylation site is already occupied, as required by claim 58 from which claim 65 depends, and at any case the non-polypeptide moiety is not an oligosaccharide moiety. Applicants therefore respectfully submit that the term "a non-peptide moiety" and the term "attachment group" is clear and definite, and request the rejection of claim 65 be withdrawn.

In view of the above, Applicants believe all claims pending in this application are clear and definite. Accordingly, withdrawal of the rejections under 35 USC §112 second paragraph is respectfully requested.

Rejection under 35 USC §102(b)

Claims 58-67 and 69-72 were rejected under 35 USC §102(b) as allegedly anticipated by Sasaki *et al.*, US Pat No. 5,218,092 (herinafter "Sasaki"). Claims 60 and 66-72 are cancelled herein, rendering the rejection of these claims moot. The rejection of pending claims 58-59 and 61-65 is respectfully traversed.

Claim 58 as amended herein is directed to a method for altering the glycosylation profile of a mature form of a polypeptide of interest, the method comprising preparing a nucleic acid comprising a nucleotide sequence encoding a peptide-extended polypeptide with the primary structure NH_2-X-Pp-COOH, wherein NH_2 and COOH represent the N-terminus and the C-terminus of the peptide-extended polypeptide, respectively; X is the sequence of a peptide addition 1-30 consecutive amino acids in length, wherein X comprises or contributes to an *in vivo* N-glycosylation site; and Pp is the sequence of the mature form of the polypeptide of interest, wherein X and Pp are linked by a peptide linkage; and expressing the nucleic acid in a glycosylating host cell to provide a peptide-extended glycosylated polypeptide; wherein the peptide-extended glycosylated polypeptide exhibits an altered glycosylation pattern compared to that of the mature form of the polypeptide of interest when expressed under the same conditions. The rejected dependent claims all ultimately depend from claim 58 and thus incorporate all the limitations of claim 58 as amended herein.

Sasaki describes constructing a nucleic acid encoding a mature polypeptide which contains a modification which introduces an N-glycosylation site **within** the sequence of the polypeptide of interest, that is, into amino acid positions 6-8 **within** the G-CSF polypeptide sequence, and expressing the nucleic acid in a glycosylating host cell. Sasaki does not teach constructing a nucleic acid sequence encoding a polypeptide of the formula NH_2-X-Pp-COOH, wherein X is the sequence of a peptide addition 1-30 consecutive amino acids in length, and Pp

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is the sequence of the mature form of the polypeptide of interest, wherein X comprises or contributes to an *in vivo* N-glycosylation site, and X and Pp are linked by a peptide linkage; and expressing the nucleic acid in a glycosylating host cell.

In light of the above, Applicants submit that Sasaki does not anticipate amended claim 58 and claims which depend therefrom. Accordingly, withdrawal of the rejection under 35 USC §102(b) is respectfully requested.

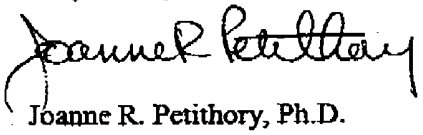
CONCLUSION

In view of the foregoing, Applicants believe the claims pending in this application are in condition for allowance. Early notification to that effect is earnestly solicited.

It is believed no fee is required for entry of this amendment, as it is submitted within the three-month period for response. However, if a fee is required, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 50-0990.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 298-5452.

Respectfully submitted,



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